Chronically Underestimated: The impact of high early life water intake rates and short-term effects for deriving health-protective drinking water criteria

US EPA Temporal Exposures Workshop
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Outline

- Background
- Evolving of Policy & Science
- Revised Methods – Multiple Durations
- Results
- Challenges
- Conclusions
Background

- Health-based drinking water guidance (HBG)

“... a concentration of a contaminant, or mixture of contaminants, that is likely to pose little or no risk to human health”
Background cont.

- **Basic equation from EPA**
  - Health endpoints other than cancer
  - Reference dose (RfD) represents a no effect dose
  - Focus - Chronic effect from chronic exposure

- **Used for drinking water health based guidance (HBG)** (MDH pre-2008)

\[
HBG (\mu g/L)_{chronic} = \frac{RfD_{chronic} \times 1000 \, \mu g/mg \times RSC}{\text{Intake Rate}_{adult/chronic}}
\]

- **Assumption:** lower chronic reference dose and long term exposure offers maximum protection
Evolving Policy & Science

Consideration of infants & children in setting standards
[NAS 1993 report: Pesticides in the Diets of Infants and Children]

- Federal Level
  - Food Quality Protection Act 1996
  - Amendments to Safe Drinking Water Act
  - 1996 EPA Science Policy Council
  - 1996 Executive Order by President Clinton

- State Level
  - 2001 Health Standards Statute (air & water)
Evolving Policy & Science

  - Additional testing on life stage differences
  - Reference values for acute, short-term, subchronic & chronic
- Estimated Per Capita Water Ingestion and Body Weight in the United States – An Update (EPA 2004)
- Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (2005)
  - Lifetime cancer slope factors
  - Age-Dependent Adjustment Factors (ADAFs)
Need for Revised Methods?

**Standard Noncancer Equation (pre-2008)**

\[ \text{HBG (µg/L)}_{\text{chronic}} = \frac{\text{RfD}}{\text{intake rate}_{\text{adult/chronic}}} \times 1000 \text{ µg/mg} \times \text{RSC} \]

**Toxicity**
- Protective of sensitive life stages?
- Protective of < chronic durations?

**Exposure**
- Protective of high short-term exposures?
- Update Water Intake Rates
GOAL

- To derive health-based drinking water criteria that adequately protects susceptible life-stages and highly exposed populations
Revised Methods

Durations (EPA 2002)

- Acute: < 24 hours
- Short-term: > 24 hours - up to 30 days
- Subchronic: > 30 days, up to ~10% of a lifespan (~90 days in typical laboratory rodent studies)
- Chronic: > ~ 10% of a life span
Revised Methods

For Each Duration (if sufficient data was available)

- **Toxicity Assessment (RfD derivation)**
  - Consider timing (e.g., life stage) & duration of dosing
  - Consider entire database in identifying ‘co-critical’ effects
  - Consider entire database in selecting type & magnitude of UFs

- **Exposure Assessment (water intake rate)**
  - Consider life-stage in calculating corresponding duration intake rates
  - Use updated age specific intake rate data

- **Relative Source Contribution (RSC)**
  - Based on “Exposure Decision Tree for RfD Apportionment” (EPA 2000)
Revised Methods

Standard Noncancer Equation

\[ HBG (\mu g/L)_{\text{duration}} = \frac{RfD_{\text{duration}} \times 1000 \, \mu g/mg \times \text{RSC}_{\text{duration}}}{\text{Intake Rate}_{\text{duration}}} \]

Where:

- \( HBG (\mu g/L) \) = Health-based Guidance value for a given duration
- \( RfD (mg/kg-day) \) = Reference Dose for a given duration (acute, short-term, subchronic, and chronic)
- \( \text{Intake Rate} (L/kg-day) \) = Water intake rate corresponding to given duration
- \( \text{RSC} \) = Relative Source Contribution, varies by duration and age group
Results

73 chemical assessments completed

- Solvents, pesticides, consumer product/personal care related chemicals, pharmaceuticals, . . .
- Short-term, subchronic and chronic values derived for 53 (~73%)
  - Remaining 20 chemicals had only subchronic & chronic (15) or only chronic value (5)
Results - Toxicity

Reference Doses

- Decreased with increasing duration
  - Short-term > Subchronic > Chronic
  - Chronic RfD was lowest for more than 90 percent (48/53)
- Exceptions - Shorter Duration RfD was lowest
  - Developmental toxicants
  - Cholinesterase inhibitors
- MDH set the final Chronic RfD to lowest RfD value
  (EPA 2002)
# Results - Toxicity

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of Chemicals</th>
<th>Geometric Mean ± GSD</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term RfD to Chronic RfD Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7 ± 3.0</td>
<td>19.1</td>
<td>24.9</td>
<td></td>
</tr>
<tr>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.8 ± 2.1</td>
<td>5.6</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Subchronic RfD to Chronic RfD Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0 ± 2.1</td>
<td>4.4</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>16&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.6 ± 1.9</td>
<td>4.2</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes chronic RfDs based on less than chronic studies  
<sup>b</sup> Limited to assessments in which comparison is across laboratory animal studies and chronic RfD is based on chronic study.
## Results - Toxicity

<table>
<thead>
<tr>
<th>Comparison</th>
<th>No. of Chemicals</th>
<th>Geometric Mean ± GSD</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term NOAEL to Chronic NOAEL Ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batke et al 2011</td>
<td>14</td>
<td>3.4 ± 3.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Zarn et al 2011 (pesticides)</td>
<td>Rat 107 Mouse 56</td>
<td>4.3 ± 4.7</td>
<td>53.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4 ± 3.6</td>
<td>23.7</td>
</tr>
<tr>
<td>Groeneveld et al 2004</td>
<td>35</td>
<td>4.9 ± 3.5</td>
<td>38.6</td>
</tr>
<tr>
<td>Kramer et al 1996</td>
<td>71</td>
<td>4.1 ± 4.4</td>
<td>46</td>
</tr>
<tr>
<td><strong>Subchronic NOAEL to Chronic NOAEL Ratio</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Batke et al 2011</td>
<td>58</td>
<td>1.4 ± 2.1</td>
<td>4.7</td>
</tr>
<tr>
<td>Zarn et al 2011 (pesticides)</td>
<td>Rat 222 Mouse 99</td>
<td>2.5 ± 3.4</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 ± 3.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Bokkers and Slob 2005</td>
<td>68</td>
<td>1.5 ± 5.3</td>
<td>22.7</td>
</tr>
<tr>
<td>Groeneveld et al 2004</td>
<td>70</td>
<td>2.3 ± 3.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Pieters et al 1998</td>
<td>149</td>
<td>1.7 ± 5.6</td>
<td>29</td>
</tr>
</tbody>
</table>
## Results – Exposure

### Age-Specific Water Intake Rates (EPA 2004)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>50th</th>
<th>90th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>birth - &lt;1 mon</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - &lt;3 mon</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - &lt;6 mon</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 - &lt;12 mon</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 3 yrs</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 - 6 yrs</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 - 10 yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 - 14 yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 - 19 yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 - 24 yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 - 54 yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 - 64 yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65+ yrs</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results - Exposure

**Water Intake Rate** (L/kg per day)

- Decreased with age* (short-term > subchronic > chronic)
- Infant intake rates much higher than adults (mean values ~10-fold higher; 90\(^{th}\) & 95\(^{th}\) percentiles ~7-fold higher)
- By ~7 yrs of age similar to adult intake rates
- Calculated time-weighted average over exposure duration

*Not unique to drinking water – skin surface area as well as food, soil, and air intakes higher in early life
Results – Exposure

Default* Duration Specific Water Intake Rates

*default value – different life-stage or duration used if chemical specific information available
Results – Exposure

Relative Source Contribution Factor (EPA 2000)

- Used to account for exposures other than ingestion of drinking water (e.g., dermal & inhalation from water use; food; soil/dust; consumer products; etc.)
- Chemical-specific or Default (range 0.2 to 0.8)
- Changes with age and exposure patterns
- Young infants have more limited exposures
- Older infants, toddlers, children and adults have more varied exposures

*Result - higher RSC for infants [Exceptions - highly volatile chemicals or baby consumer products]*
Results – HBGs

Standard Noncancer Equation

\[ \text{HBG (µg/L)}_{\text{duration}} = \text{RfD}_{\text{duration}} \times 1000 \text{ µg/mg} \times \text{RSC}_{\text{duration}} \times \text{Intake Rate}_{\text{duration}} \]

Where:

- \( \text{HBG (µg/L)} \) = Health-based Guidance value for a given duration
- \( \text{RfD (mg/kg-day)} \) = Reference Dose for a given duration
- \( \text{Intake Rate (L/kg-day)} \) = Water intake rate corresponding to given duration
  - Default: Acute/Short-term (1 – 3 month infant); Subchronic (TWA birth to 8 yrs); and Chronic (TWA birth to 70 yrs)
- \( \text{RSC} \) = Relative Source Contribution
  - Default: Acute/Short-term – 0.5 [except: highly volatile chemicals & baby consumer product (0.2) and prescription drugs (0.8)]; Subchronic and Chronic - 0.2 [except prescription drugs (0.8)]
Results – HBGs

Health-based Guidance (HBG)

- Unlike RfDs, HBGs did not decreased with increasing duration
- Chronic duration HBGs were lower than shorter duration for 28 of the 53 chemicals (~53%)
- The 7-fold difference in short-term intake rate ‘overwhelmed’ the 2-4 fold differences in RfDs
- MDH set the final Chronic HBG to the lowest HBG value
Challenges

- **Toxicity data limitations**
  - Lower quality of shorter duration studies
  - Inadequate reporting of effects at interim time points
  - Latent effects of early-life exposures

- **Exposure data limitations**
  - Early-life exposures
    - Often only have measure of maternal exposure in laboratory animal studies
    - Cumulative exposures to inform RSC, especially for high short-term exposures

- **Resources**
  - Time intensive – resulting in fewer chemicals assessed
Conclusions

- Results support recommendations of EPA 2002 report (i.e., calculation of multiple duration RfDs)
- Results demonstrate importance (necessity?) of evaluating shorter durations to ensure protectiveness
- In absence of shorter duration RfDs - use chronic RfD may be reasonable option for screening level assessment (option suggested by EPA 2002)
Questions?

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Methodology can be found at:

Health-based Guidance values can be found at:
http://www.health.state.mn.us/divs/eh/risk/guidance/gw/table.html